

88-107203

B7

(12) UK Patent Application (19) GB (11) 2 195 891 (13) A

(43) Application published 20 Apr 1988

(21) Application No 8723120

(22) Date of filing 2 Oct 1987

(30) Priority data

(31) 816065

(32) 6 Oct 1986

(33) US

(51) INT CL*

A61K 47/00 9/20 33/06 37/22

(52) Domestic classification (Edition J):

A5B 180 230 232 23Y 28Y 272 273 274 275 27Y 285
28Y 301 303 30Y 340 343 34Y 402 40Y 481 482 48Y
586 58Y 827 832 833 KC
U18 1318 1330 A5B

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(56) Documents cited

GB A 2122489 GB 1336373
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GB 1380208 GB 0932378

GB 0840155

(58) Field of search

A5B
Selected US specifications from IPC sub-class A61K

(54) Improving palatability of pharmaceutical chewable tablets

(57) Lipid-containing solid pharmaceutical compositions comprise:

- (a) from about 10% to about 50% of a lipid material (e.g. hydrophilic saccharide);
- (b) from about 10% to about 50% of a dispersant material;
- (c) from about 0.1% to about 3% of a nonionic emulsifier having an HLB of at least about 10; and
- (d) a safe and effective amount of a pharmaceutical active material.

wherein the average HLB of all emulsifiers in the composition is at least about 8.

The compositions as described are antacid chewable tablets wherein the lipid formulation is to improve palatability, and effective dispersion in the mouth and stomach.

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SPECIFICATION

Efficacious lipid-containing pharmaceutical compositions

5 BACKGROUND OF THE INVENTION

This invention relates to palatable solid pharmaceutical compositions useful in humans and other animals. In particular, it relates to highly efficacious compositions comprising a pharmaceutical active in a lipid-containing matrix. Preferred compositions further relate to highly palatable tablets, which are chewable or liquify in the mouth, useful for the treatment of gastrointestinal disorders.

10 Pharmaceutical compositions may be produced in a variety of dosage forms, depending upon the desired route of administration of the active material. Oral dosage forms, for example, include such solid compositions as tablets, capsules, granules and bulk powders, and such liquid compositions as solutions, emulsions, and suspensions. The particular dosage form utilized may, of course, depend upon such factors as the solubility and chemical reactivity of the pharmaceutical active. Further, the dosage form may be selected so as to optimize delivery of the pharmaceutical active and/or consumer acceptability of the composition.

15 Tablet compositions offer many advantages, including ease of product handling, chemical and physical stability, portability (in particular, allowing ready availability to the consumer when needed), aesthetic acceptability, and dosage precision, (i.e., ensuring consistent and accurate doses of the pharmaceutical active). However, liquid formulations may offer advantages in the treatment of certain disorders, such as disorders of the upper gastrointestinal tract, wherein delivery of an active material dissolved or dispersed in a liquid ensures rapid and complete delivery to the afflicted area. In an effort to obtain the therapeutic advantages associated with liquid formulations as well as the broad advantages associated with solids, many chewable tablet 20 formulations have been developed and described in the pharmaceutical literature. See, for example, L. Lachman, et al., *The Theory and Practice of Industrial PharmacY* (2nd Ed., 1978).

25 Many such compositions are antacids, for the treatment of gastric hyperacidity and related disorders. Many antacid compositions in liquid form are quite effective due to the ready availability of the antacid active material (which is typically water-insoluble) suspended in a liquid vehicle. 30 There are also many solid antacid formulations, typically chewable tablets, which are designed to deliver small particles of antacid active to the stomach after chewing of the tablet.

35 Chewable tablets, such as antacid tablets, often contain high levels of mannitol or similar binders as well as methylcellulose, glycine, or other binding agents. Other chewable tablets are described in the literature containing fatty materials. See, for example, U.S. Patent 4,230,693, Izzo, et al., issued October 28, 1980, U.S. Patent 4,327,076, Puglia, et al., issued April 27, 1982, U.S. Patent 4,327,077, Puglia, et al., issued April 27, 1982, U.S. Patent 4,533,543, Morris, et al., issued August 6, 1985, and U.S. Patent 4,581,381, Morris, et al., issued April 8, 1986.

40 Many such solid antacid formulations fail to offer the equivalent efficacy to liquid antacid compositions, for a variety of reasons. For example, the tablets may be incompletely chewed due to poor palatability of the composition. This problem is particularly acute with antacids, since the active materials in these products often have a metallic flavor and an astringent, chalky mouth feel. Such compositions may also have a gummy texture, and are subject to "taste fatigue", i.e., the composition is perceived to be less palatable after ingestion of multiple doses. 45 Further, the binders and other materials used in such chewable tablets may prevent rapid and effective delivery of active materials to the stomach.

50 It has been found that tablet formulations containing lipid materials and selected emulsifiers are highly palatable and effective compositions for the delivery of pharmaceutical active materials. Such compositions, for example, are more effective than similar lipid-containing compositions known in the art. In particular, such compositions containing selected high HLB emulsifiers as further defined herein, afford improved efficacy when compared to similar compositions not containing the selected emulsifiers.

SUMMARY OF THE INVENTION

55 The present invention provides lipid-containing solid pharmaceutical compositions comprising:
(a) from about 10% to about 50% of a lipid base material;
(b) from about 10% to about 50% of a dispersant material;
(c) from about 0.1% to about 3% of a nonionic emulsifier having an HLB of at least about 10; and
60 (d) a safe and effective amount of a pharmaceutical active material; wherein the average HLB of all emulsifiers in said composition is at least about 8. Preferably the average HLB of all emulsifiers in the composition is at least about 10.

65 Among the preferred lipid-containing compositions of this invention are chewable tablets useful for the treatment of upper gastrointestinal disorders, such as an antacid composition containing from about 10% to 65% of an acid neutralizing material. The present invention also provides

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coated unit dosage compositions which comprise the lipid-containing solid compositions of this invention coated with a solid coating material.

DESCRIPTION OF THE INVENTION

5 The compositions of the present invention contain a pharmaceutical active material in a vehicle containing a lipid base material, a dispersant material and an emulsifier. In addition, the compositions of the present invention may contain optional pharmaceutically-acceptable components which may modify their physical characteristics and/or therapeutic effects. All components of the present compositions must, of course, be pharmaceutically-acceptable. As used herein, a "pharmaceutically acceptable" component is one which is suitable for use with humans and/or other animals without undue adverse side effects (such as toxicity, irritation and allergic response) commensurate with a reasonable benefit/risk ratio.

10 The present invention provides lipid-containing solid pharmaceutical compositions comprising:

- (a) from about 10% to about 50% of a lipid base material;
- 15 (b) from about 10% to about 50% of a dispersant material;
- (c) from about 0.1% to about 3% of a nonionic emulsifier having an HLB of at least about 10; and

(d) a safe and effective amount of a pharmaceutical active material;

20 wherein the average HLB of all emulsifiers in said composition is at least about 8. Except as otherwise stated, all percentages set forth herein are by weight of total composition.

Further, as used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components employed.

25 Preferably, the lipid base material is present in the present compositions at a level of from about 20% to about 40%, more preferably from about 25% to about 40%. Also preferably, the dispersant material is present at a level of from about 20% to about 40%, more preferably from about 20% to about 35%. The nonionic emulsifier is preferably present at a level of from about 0.5% to about 2%, more preferably from about 0.6% to about 1.5%. Specific components, and optional materials useful in these chewable tablet compositions are further described below.

30 35 The average HLB of all emulsifiers incorporated in the present compositions (including the essential nonionic emulsifiers and any optional emulsification materials) is at least about 8, preferably at least about 10. As used herein, the term "average HLB" refers to the weighted average of the HLB of all emulsifiers in the composition, i.e.,

$$40 \text{ total HLB} = \frac{HLB_1 \times Wt\% E_1 + HLB_2 \times Wt\% E_2 + \dots + HLB_n \times Wt\% E_n}{Wt\% E_1 + Wt\% E_2 + \dots + Wt\% E_n} \quad 40$$

These compositions may be provided in unit-dosage form, as compressed or molded tablets. 45 Compressed tablets are produced by compression of tablet components, in a solid or semi-solid state mixture. Molded tablets are produced by forming a liquid product mass, i.e., by melting the fatty carrier materials and admixing the other components, followed by pouring into tablet-form molds, and cooling to a solid state. Although these compositions may be swallowed whole or in part without chewing, the present compositions are preferably comprised so as to facilitate 50 chewing and/or melting in the mouth. The present compositions thereby facilitate dispersion of the pharmaceutical active material in saliva and (after swallowing, ultimately) in the gastric fluids of the stomach.

The molded uncoated compositions of this invention, while in a liquid mixture (melted) at approximately 40°C, preferably have a viscosity of less than about 12,000 centipoises (cps), as measured by a Brookfield Viscometer (Model RVT/2 Helipath, spindle C, at 10 rpm). More preferably, the present compositions have a viscosity of less than about 7000 cps. Such a viscosity may be obtained by selection of particle size of the pharmaceutical actives material and dispersant material, and by incorporation of selected optional components, as described below. Preferably, the mean particle size of such particulate materials is from about 4 microns to about 60 10 microns, more preferably from about 6 microns to about 10 microns. Also preferably, less than about 10% of the particulates have a particle size greater than about 30 microns. (As used herein, "particle size" of a particulate refers to the diameter of a sphere having a volume equal to that of said particulate.) Compositions having such preferred viscosities are described in copending U.S. Patent Application Serial No. (P&G Case 3572), filed October 6, 1986.

65 Also preferably, the compositions of this invention contain less than about 1% of materials that

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are liquid at ambient conditions in addition to any liquid components in the lipid material. More preferably, these compositions contain less than about 0.5% of such additional liquid materials.

Essential Components

5 As described above, the present chewable tablet compositions contain four essential components: a lipid base material, a dispersant material, a nonionic emulsifier material, and a pharmaceutical active material. These compositions may also contain optional components, such as other emulsifiers, tempering aids, flavorants and colorants.

Lipid Material:

The compositions of the invention contain one or more materials, (herein individually and in mixtures referred to as "lipid materials") that are substantially water-insoluble, inert, pharmaceutically-acceptable hydrocarbon fats or oils, or their derivatives, or mixtures thereof. The lipid materials useful herein preferably have a melting point of from about 26°C (80°F) to about 43°C (110°F), more preferably from about 30°C (86°F) to about 38°C (100°F), more preferably from about 32°C (90°F) to about 37°C (99°F). The particular lipid material employed may be selected in order to obtain desired product characteristics. These characteristics include such factors as rheology (mouth feel), appearance, flavor and compatibility with the pharmaceutical active.

Among the lipid materials useful herein are those which are commercially available and commonly used in confectionery and other food products. Such lipid materials include, for example, cocoa butter, hydrogenated tallow, hydrogenated vegetable oils, and derivatives and mixtures thereof. Hydrogenated vegetable oils (such as hydrogenated palm kernel oil), cocoa butter, and cocoa butter substitutes are among the preferred useful lipid materials. Lipid materials among those useful in this invention are described in the following documents, all incorporated by reference herein: U.S. Patent 2,903,363, Farr, issued September 8, 1959; British Patent Specification 827,178, Best et al., published February 3, 1960; U.S. Patent 3,012,891, Best et al., issued December 12, 1961; U.S. Patent 3,093,480, Arnold, issued June 11, 1963; U.S. Patent 3,492,130, Harwood, issued January 27, 1970; U.S. Patent RE 28,737, Yetter, reissued March 16, 1976; European Patent Application 23,082, Cotton et al., published January 28, 1981; U.S. Patent 4,276,322, Padley et al., issued June 30, 1981; U.S. Patent 4,283,436, Soeters et al., issued August 31, 1981; U.S. Patent 4,364,868, Hargreaves, issued December 21, 1982; and U.S. Patent 4,581,381, Morris et al., issued April 8, 1986; and U.S. Patent 4,594,259, Baker et al., issued June 10, 1986.

Particularly preferred lipid materials are those that melt sharply at about 33°C (91°F). Such fats which melt "sharply" are those with melting profiles similar to cocoa butter, which is a solid at ambient temperatures, but is entirely liquid at a point just below mouth temperature (approximately 34°C). A particularly preferred lipid material is described in U.S. Patent 4,594,259, Baker et al., issued June 10, 1986. Solid pharmaceutical compositions containing these particularly preferred materials are described in U.S. Patent Application Serial No. (P&G Case 3570).

40 filed October 6, 1986.

Such particularly preferred compositions contain one or more materials, herein "lipid base materials", which together with all other mono-, di- and tri-glycerides (if any) in the compositions form the "lipid component" of the chewable tablet compositions. The lipid component of the present composition thus preferably contains certain key triglycerides: saturated-oleic-saturated ("SOS"), saturated-unsaturated-unsaturated ("SUU"), unsaturated-unsaturated-unsaturated ("UUU"), saturated-lineolic-saturated ("SLS") saturated-saturated-oleic ("SSO"), and saturated-saturated-saturated ("SSS") triglycerides, i.e., referring to the chemical structure of the fatty acid moiety of each glyceride in the key triglyceride. As used herein, "S" refers to the stearic ("St") or palmitic ("P") fatty acid residues of the glyceride molecule and ("U") refers to the oleic ("O") or linoleic ("L") fatty acid residues of the glyceride molecule.

Specifically, the lipid component of such particularly preferred composition contains at least about 70% of SOS triglycerides, and from about 4% to about 20% of combined SUU/UUU/SLS triglycerides, where the St:P weight ratio is about 0.8 or less. (These percentages are by weight of the lipid component, not by weight of total composition.) Preferably the lipid component

55 contains about 8% or less of SLS triglycerides, about 9.5% or less of SSO triglycerides, about 2.5% or less of SSS triglycerides, and about 4% or less of other triglycerides. The lipid component of the present invention preferably is comprised entirely of a fat having a low St:P ratio (about 0.2 or less). A POP fat is particularly preferred. A preferred source of POP fat is through a triple stage solvent fractionation of palm oil. This process is described in U.S. Patent

60 4,588,604, Baker et al., issued May 13, 1986 (incorporated by reference herein).

Dispersant Material:

The compositions of this invention also contain a hydrophilic material, herein "dispersant material", which serves to aid dispersion of the pharmaceutical active and other materials of the composition in the mouth and/or stomach. Many dispersants among those useful herein are

known in the pharmaceutical arts. Dispersant materials among those useful herein include sugars (such as sucrose, mannitol, sorbitol, dextrose, maltose, and lactose), starches and starch derivatives (such as corn starch and maltodextrin), microcrystalline cellulose, and mixtures thereof.

Among the preferred dispersant materials useful herein are sucrose, sorbitol, mannitol, and mixtures thereof.

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Nonionic Emulsifier.

The compositions of this invention also contain one or more nonionic emulsification materials (herein individually and in mixtures referred to as "nonionic emulsifiers"). Emulsifiers may be

10 characterized by their hydrophilic/lipophilic behavior. This behavior can be numerically expressed for a given emulsifier by its hydrophilic-lipophilic balance (HLB). The HLB value of an emulsifier can be determined experimentally or computed (particularly for polyoxyethylene ethers) from its structural formula. In general, emulsifiers with high HLB values are more hydrophilic, and tend to favor formation of oil-in-water emulsions, as opposed to emulsifiers with lower HLB values.

15 The nonionic emulsifiers of this invention have an HLB of at least about 10, preferably at least about 11. Mixtures of such nonionic emulsifiers are preferred, particularly mixtures wherein at least one emulsifier has an HLB of at least about 12, preferably at least about 15.

20 Many such emulsifiers are known in the pharmaceutical arts. See, for example, M. Rieger, "Emulsions", *The Theory and Practice of Industrial Pharmacy* (L. Lachman, et al., ed. 1976), incorporated by reference herein. Emulsifiers among those useful herein are also described in 20 McCutcheon's *Emulsifiers and Detergents, North American Edition* (1983), incorporated by reference herein.

25 In particular, nonionic emulsifiers among those useful herein include polyethoxylated esters, polyglycerol esters, sorbitan esters and ethoxylates, sucrose esters, and mixtures thereof. Many such nonionic emulsifiers are commercially available. Such emulsifiers include, for example: Caprol PGE860 (decaglycerol mono-dioleate), manufactured by Capital Cities Products Co.; Hodag PSMS-20 (polyoxyethylene sorbitan) and Hodag SVO-9 (polyoxyethylene sorbitan 20 monoooleate), manufactured by Hodag Chemical Corp.; Liposorb L-20 (polysorbate 20), Liposorb O-20 (polysorbate 80), and Liposorb S-20 (polysorbate 60), manufactured by Lipo Chemicals, Inc.; 30 Pluronic F69 (block copolymer of propylene oxide and ethylene oxide), manufactured by BASF Wyandotte Corp.; Santone 8-1-S (polyglycerol esters of fatty acids), manufactured by Durkee Industrial Foods Group of SCM Corp.; and Tween 20 (polyoxyethylene 20 sorbitan monostearate), Tween 60 (polyoxyethylene 20 sorbitan monostearate), Tween 80 (polyoxyethylene 20 sorbitan tristearate, polysorbate 65) and Myrij 52 (polyoxyl 40 stearate), manufactured by ICI Americas, Inc.

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Pharmaceutical Active Material.

The present compositions also contains a "pharmaceutical active material", i.e., a material which is intended to have a physiologic effect on the human or lower animal to whom the

40 composition is administered. Pharmaceutical active materials particularly useful in the chewable tablet formulations of this invention include those actives which become bioavailable and/or have their site of action in the mouth or stomach. The rapid dispersion of such active materials in the saliva, as afforded by the present chewable tablets, is particularly advantageous. Among such active materials are the analgesics, such as aspirin and acetaminophen, and materials useful in 45 the treatment of gastrointestinal disorders.

45 Among the pharmaceutical active materials particularly useful in the compositions of this invention are the bismuth salts and the metallic antacid salts. Such bismuth salts include, for example, bismuth aluminate, bismuth citrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, bismuth subsalicylate, and mixtures thereof. A particularly preferred bismuth salt is 50 bismuth subsalicylate. Metallic antacid salts useful herein include, for example, aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxycarbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium 55 glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, and mixtures thereof. Aluminum magnesium hydroxide sulfate (also known as magaldrate) is a preferred metallic antacid salt useful herein.

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Optional Components

60 The compositions of this invention may also contain pharmaceutically-acceptable optional components which modify the physical & d/or therapeutic effects of the composition. Such optional components may include, for example, emulsifiers, binders lubricants glidants colorants flavors and sweeteners. Such components are generally described in Marshall, "Solid Oral Dosage Forms" *Modern Pharmaceutics Volume 7* (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein, and W. Gunzel, et al., "Tablets", *The Theory and Practice of*

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Industrial Pharmacy (L. Lachman, et al., editors, 2 ed.), 321-358 (1976), incorporated by reference herein.

In addition to the essential nonionic emulsifiers described above, the compositions of this invention may also contain one or more low-HLB emulsifiers (i.e., emulsifiers having HLB values less than about 10). These emulsifiers are preferably included in order to improve rheology of the compositions in the mouth (''mouth feel''). Preferably, the present compositions contain from about 0.1% to about 1.0%, preferably from about 0.1% to about 0.5% of a low-HLB emulsifier. Preferably, the such low-HLB emulsifiers have an HLB of from about 4 to about 10, preferably from about 6 to about 10. Also preferably, the present compositions are essentially free from 10 (i.e., containing less than about 0.1% of) emulsifiers having HLB values less than about 4.

The type and amount of emulsifiers useful in the present invention may be selected in order to obtain compositions with preferred melting viscosities, as described above. Such emulsifiers and other optional components useful in preferred compositions of this invention are described in U. S. Patent Application Serial No. (P&G Case 3572), filed October 6, 1986, incorporated by 10 reference herein.

As will be appreciated by those skilled in the art, the lipid base material of the present composition may be present in any of a number of crystal forms, or polymorphs. For compositions wherein POP fat is utilized as the lipid base material, it is preferred that the fat be present in the beta-prime-2 or beta-3 polymorph state. The crystal structure of the lipid base 20 material useful herein may be affected by a variety of factors, as can be ascertained by one of skill in the art. Such factors include the presence of solids in the composition, the presence of emulsifiers, the processing conditions (particularly cooling temperatures and rates), and the particular lipid base material employed.

A preferred optional component in molded tablets of this invention (i.e., compositions that are 25 formed upon solidification of a heated liquid composition after pouring into a suitable mold) is a ''tempering aid''. Such materials aid in the formation of a desired crystal structure for the lipid components of the present composition, such that the composition has a desired uniform, smooth, non-gritty texture and appearance. Tempering aids are preferably included at a level of from about 0.2% to about 2%. Among tempering aids useful herein are mixtures of mono- and 30 diglycerides, such as Dur-Ern 127 (manufactured by Durkee Foods, Division of SCM Corporation) and triglyceride mixtures, such as Cessa 60 (manufactured by Friwessa).

Other preferred optional components useful herein include flavorants and sweeteners, at levels of from about 0.01% to about 1.0%. Colorants may be included at typical levels of from about 0.01% to about 0.5%.

35 As stated above, the present compositions may be coated, to provide a coated unit dosage form. The coated compositions of the invention comprise a lipid-containing composition of this invention, covered with from about 10% to about 50%, preferably from about 10% to about 30%, (by weight of final coated composition) of a solid, water-soluble coating material having a melting point greater than about 45°C. Such coated compositions preferably are in unit-dosage 40 form, i.e., containing an amount of pharmaceutical active material suitable for administration to a human subject, in one dose, according to good medical practice. The coated compositions of this invention preferably contain from about 0.5 to about 2.5 grams, preferably from about 1.0 to about 2.0 grams, of the lipid-containing composition of this invention. Coating materials, and methods, among those useful herein are well known in the pharmaceutical arts. See, for 45 example, W. Gunzel, et al., ''Tablets'', *The Theory and Practice of Industrial Pharmacy* (L. Lachman, et al., editors, 2d ed.) 321-358 (1978), incorporated by reference herein. Preferred coatings and materials are described in U.S. Patent Application Serial No. (P&G Case 3573), filed October 6, 1986, incorporated by reference herein.

50 Methods

The chewable tablet compositions of this invention may be made by either compression or molding techniques. Compression techniques generally involve admixture of materials in an essentially dry state, followed by compression in a desired tablet form, under pressure. Molding techniques generally involve admixture of components in an essentially liquid form, followed by 55 pouring into a desired tablet mold and cooling to a solid, or semi-solid form. The compositions of this invention are preferably in molded form.

The lipid base material used in molded compositions of the present invention is preferably in a stable crystal form, such that the composition is comprised of stable crystals less than about 5 microns, preferably from about 1 to about 2 microns, in size, and the composition has a 60 uniform, smooth, non-gritty appearance and rheology. Such parameters, and the factors which influence them, are analogous to parameters that are well known in the chocolate confectionary arts. As discussed above, materials may be added to the present compositions which aid in obtaining a preferred, stable crystal structure, or ''temper''. Processing conditions for making molded compositions are also critical, and are preferably controlled to yield a preferred tempered 65 composition. Such ''tempering'', for compositions utilizing POP fat as a lipid base material,

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typically involves cooling of the product in liquid form, to a temperature of approximately 22°C. This cooling induces formation of a variety of crystals of different melting points. The composition is then heated, with stirring, to approximately 29.5°C., melting the undesired lower-melting crystals. (The fluid product at this point is thereby "seeded" with higher-melting crystals.) The 5 fluid product is then poured into molds, vibrated to remove air bubbles, and slowly cooled to solidify the composition into a product having the desired crystal form.

The following non-limiting Examples illustrate the compositions, processes and uses of the present invention.

10 EXAMPLE 1

A coated antacid composition according to this invention was made comprising:

<u>Component</u>	<u>% Bulk Composition</u>	<u>% Final Tablet</u>	
15 POP fat	34.009	28.908	15
sucrose	31.640	26.894	
magaldrate ²	31.640	26.894	
20 simethicone	0.991	0.842	20
Span 80 ³	0.478	0.406	
Tween 60 ⁴	0.148	0.126	
25 sucrose monoester ⁵	0.487	0.414	25
sodium stearoyl			
lactylate ⁶	0.009	0.008	
30 Dur-Em 127 ⁷	0.498	0.423	30
peppermint oil	0.100	0.085	
	100.000		
35 (Coating)			
Neosorb P100T ⁸		8.700	35
lycasin		4.100	
mannitol		2.200	
40		100.000	40

1. lipid base material, comprising approximately 88% SUS triglyceride, with an St:P ratio of approximately 0.13

45 2. aluminum magnesium hydroxide sulfate, antacid active material

3. sorbitan monooleate emulsifier, HLB = 4.3, manufactured by ICI Americas, Inc.

4. polyoxyethylene (20) sorbitan monooleate emulsifier, HLB = 14.9, manufactured by ICI Americas, Inc.

5. emulsifier, HLB = 15.0

50 6. emulsifier, HLB = 9.0

7. tempering aid mixture of mono- and diglycerides, HLB = 2.8, manufactured by Durkee Foods, Division of SCM Corporation.

8. fine sorbitol powder, manufactured by The Roquette Corporation.

A composition according to this invention was made by admixing the magaldrate and sugar,

55 and heating to approximately 40°C. Separately, approximately 55% of the POP fat was melted at approximately 40°C., and approximately 10% of the Span 80 was added, and mixed. The POP-fat mixture was then added to the active/sugar mixture, maintaining the temperatures at approximately 40°C., and mixed for approximately 45 minutes. The mixture was passed through a 4-roll roller mill, at approximately 300 psi, to ensure adequate contact and mixture of the lipid base

60 material and the powdered materials. The 4 mill rollers were at temperatures of approximately 27°C, 21°C, 21°C and 21°C, respectively.

Separately, the remaining portion of POP (approximately 45% of the original quantity) was admixed with the remaining portion of Span 80 (approximately 90% of the original quantity), the Dur-Em, and the sodium stearyl lactylate emulsifier, for approximately 10 minutes, at a temperature of approximately 50°C. The POP milled mixture was then added to this mixture, and mixed

for approximately 15 minutes. The sucrose monoester and Tween 60 were dissolved in ethanol, and then added to the composition. The peppermint oil and simethicone were then added, and the compositions mixed for approximately 45 minutes, maintaining the temperature at approximately 50°C. The composition was then cooled to approximately 22°C, and tempered by rapidly 5 raising the temperature to approximately 29.5°C, forming seed crystals. The composition was then poured into tablet molds and allowed to solidify. The average tablet weight was approximately 2.2 g.

The tablets were then coated by placing them in a conventional coating pan apparatus. A portion of the lycasin was added, and the tablets evenly wetted. The mannitol was then added, 10 and the tablets mixed for approximately 10 minutes, and then dried for approximately one hour. The tablets were then coated with lycasin and Neosorb, following the same procedure, and dried for approximately 12 hours.

A coated antacid tablet, comprised as above, was administered to a human subject experiencing heartburn, and were effective in reducing the severity of symptoms. The average HLB of the 15 lipid containing core composition of this Example is calculated to be approximately 8.1.

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EXAMPLE II

A coated antacid composition according to this invention is made comprising:

	<u>Component</u>	<u>% Bulk Composition</u>	<u>% Final Tablet</u>	
20	POP fat	28.0	23.80	
	sucrose	15.0	12.75	
25	sorbitol	15.0	12.75	25
	calcium carbonate	40.0	34.00	
	sucrose monoester	1.0	0.85	
30	Tween 60	0.5	0.43	30
	flavorant	0.5	0.42	
		100.00		
35	(Coating)			35
	sorbitol		3.00	
40	corn syrup		1.00	40
	sucrose		10.50	
	maltrin		0.50	
45			100.00	45

A coated antacid composition, comprised as above, is made by a method analogous to that described in Example 1. The tablets are formed into unit dosage tablets, containing approximately 2.2 grams of the lipid-containing composition. The average H LB of the lipid-containing 50 core composition of this Example is calculated to be approximately 14.9.

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EXAMPLE III

A coated antacid composition according to this invention was made comprising:

	<u>Component</u>	<u>% Bulk Composition</u>	<u>% Final Tablet</u>	
5	POP fat	35.942	30.000	
5	sucrose	26.119	21.800	5
	magaldrate	35.703	29.800	
10	Cessa 60 ¹	0.994	0.830	
10	Myrj 52 ²	0.503	0.420	10
	Caprol PCE 860 ³	0.395	0.330	
	Polyaldo HCDS ⁴	0.252	0.210	
15	flavorant	<u>0.092</u>	0.077	15
		100.000		
20	(Coating)			20
	sorbitol solution ⁵		10.700	
	lycasin		1.060	
25	mannitol		4.023	25
	Klucel EF ⁶		<u>0.750</u>	
			100.000	
30	1. triglyceride mixture, tempering aid, manufactured by Friwessa			30
	2. polyoxyl (40) stearate, nonionic emulsifier, HLB = 16.9, manufactured by ICI Americas, Inc.			
	3. decaglycerol mono-dioleate nonionic emulsifier, HLB = 11.0, manufactured by Capital City Products Co., division of Stokely-Van Camp, Inc.			
35	4. hexaglycerol distearate nonionic emulsifier, HLB = 7.0, manufactured by Clyco, Inc.			35
	5. 70% solution			
	6. hydroxypropyl cellulose gum, manufactured by Hercules Chemical Company.			
	A coated composition, comprised as above, was made by a method analogous to that described in Example 1. The average HLB of the lipid-containing core composition of this			
40	Example is calculated to be approximately 12.7.			40

EXAMPLE IV

An uncoated composition according to this invention is made comprising:

	<u>Component</u>	<u>% by Weight</u>	
45	POP fat	34.6	45
	mannitol	15.76	
50	bismuth subsalicylate	25.95	50
	calcium carbonate	20.00	
	hexaglycerol distearate	0.25	
55	polyoxyl (40) stearate	0.50	55
	sucrose monoester	0.48	
	flavorant	1.60	
60	sweetener	0.20	60
	colorant	0.26	

Unit dosage tablets, comprised as above, are made containing approximately 1.1 grams of composition per tablet. Two tablets are administered to a human subject experiencing nausea,

lessening the severity of symptoms. The average HLB of the composition of this Example is calculated to be approximately 14.6.

CLAIMS

- 5 1. A solid pharmaceutical composition comprising: 5
(a) from about 10% to about 50% of a lipid base material;
(b) from about 10% to about 50% of a dispersant material;
(c) from about 0.1% to about 3% of a nonionic emulsifier having an HLB of at least about 10;
and
- 10 (d) a safe and effective amount of a pharmaceutical active material; 10
wherein the average HLB of all emulsifiers in said composition is at least about 8.
2. A solid pharmaceutical composition according to Claim 1, wherein said nonionic emulsifier has an HLB of at least about 11.
3. A solid pharmaceutical composition according to Claim 2, wherein the average HLB of all 15
emulsifiers in said composition is at least about 10. 15
4. A solid pharmaceutical composition according to Claim 2, containing at least two said nonionic emulsifiers.
5. A solid pharmaceutical composition according to Claim 1, wherein said lipid base material is present at a level of from about 25% to about 40%.
- 20 6. A solid pharmaceutical composition according to Claim 5, wherein said dispersant material is present at a level of from about 20% to about 35%. 20
7. A solid pharmaceutical composition according to Claim 6, wherein said nonionic emulsifier is present at a level of from about 0.6% to about 1.5%.
8. A solid pharmaceutical composition according to Claim 7, containing less than about 0.1% 25
of emulsifiers having HLB values less than about 4. 25
9. A solid pharmaceutical composition according to Claim 7 wherein said pharmaceutical active material is useful in the treatment of gastrointestinal disorders.
10. A solid pharmaceutical composition according to Claim 9, wherein said pharmaceutical active material is a metallic antacid salt.
- 30 11. A solid pharmaceutical composition according to Claim 10, wherein said metallic antacid salt is magaldrate. 30
12. A solid pharmaceutical composition according to Claim 9, wherein said pharmaceutical active material is a bismuth salt.
- 35 13. A coated pharmaceutical composition, in unit dosage form, comprising from about 50% to about 90% of a composition according to Claim 1, and from about 10% to about 50% of a coating material. 35

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